REMARKS/ARGUMENTS

The invention in this application involves the provision of a standard diluent for use in detecting target analytes in an immunoassay, in which two or more different target analytes are to be detected in a multiplex (i.e., simultaneous) assay. In preferred versions, the assay is aimed at detecting up to fifty or 100 different target analytes, preferably from two to fifty, or three to twenty, or four to fifteen, and in one example, eight different target analytes. The standard diluent of a biological fluid that is of a type that normally contains all the target analytes to be detected but, as present in the assay kit, is substantially free of these analytes.

The standard diluent that is substantially free of these target analytes is prepared from the appropriate biological fluid in one of two ways. In one embodiment the biological fluid initially contains the target analytes, but they are substantially removed, for example by affinity chromatography, to produce the standard diluent that is included in the kit. In the other embodiment, the biological fluid is obtained from a host (for example, a human) whose biological fluid is already substantially free of the desired target analytes.

As stated in the specification, the term "substantially free" means that the target analytes either are undetectable by immunoassay methods, or that they are detectable, but are present in an amount below a selected sensitivity threshold.

Such standard diluents make possible the multiplex analyses for a plurality of target analytes ranging upwards from two to one hundred, or some intermediate number, as described in the specification, which contains an example showing the use of a standard diluent according to the invention in a procedure for detection of eight target analytes.

Claims 1-31 and 49-60 are under examination in this application. Claim 1 has now been amended to incorporate the two embodiments of claims 2 and 3, that is, that the target analytes are substantially removed from a sample by affinity chromatography to produce the standard diluent that is included in the kit, or that the biological fluid is obtained from a host (for example, a human) whose biological fluid is already substantially free of the desired target analytes.

A new rejection has been issued, namely of claims 1, 5, 6 and 9 over Williams et al. in view of Boguslaski et al. Applicants note that claims 2 and 3, which are now incorporated into claim 1, were not included in this rejection, so that their inclusion into

claim 1 should make that claim and those dependent on it patentable over this combination of references. In any case, Williams et al. disclose only a process in which a standard diluent is prepared that has had all steroids removed in order to prevent interference with a steroid, and thus is not relevant to the present claims. Boguslaski et al. is cited only for its general disclosure of kits.

The previous rejection of Claims 1-3, 5-8, 11, 12, 15-17 and 49 as anticipated by Tamarkin et al. is maintained.

Applicants respectfully controvert this rejection. As discussed in the previous amendment, and as accepted by the Examiner in withdrawing the rejection of these claims as anticipated by Tamarkin et al., this reference teaches the removal of only a single target analyte (IL-1 or IL-2) from a serum solution. Throughout the specification Tamarkin et al. refer to "a cytokine" and "the cytokine" but do not use the plural form. In column 16 (lines 37-42) Tamarkin et al. refer to preabsorption of IL-1 or IL-2 from a serum solution, but not of both. This statement is repeated at col. 17 lines 39-43. At col. 17 lines 14-22, parallel immunoassays are conducted for each of IL-1 and IL-2; note the term "both the IL-1 and IL-2 EIAs".

Barrera et al. is now cited as teaching removal of two cytokines (IL-1ÿ and TNF) from a biological fluid to be used as diluent in cytokine assays, to provide for a matrix similar to the sample.

However, Barrera et al., like Tamarkin et al., prepare a standard diluent that is missing only a single analyte - not a plurality of analytes. See, for example, page 100, right hand column ("The blood compartment contained ^{125}I-labeled recombinant human IL-1ÿ or TNF, while the plasma in the dialysate compartment did not contain radiolabeled cytokine." (emphasis added). All of the experimental work in this publication describes the use of dialysis to remove a single cytokine from a blood sample and compare the resulting specimen with the original. No removal of two or more cytokines or production of a sample lacking two or more cytokines was carried out. This reference does not add the missing factor to Tamarkin et al.

Nonetheless, the examiner maintains that Barrera et al. disclose preparation of a standard diluent that contains more than one target analyte, and points to the use of the term "cytokines" as evidence of this. Applicants submit, however, that despite the use of the plural

term "cytokines", this reference discloses only a standard diluent lacking a single cytokine; the language relied on by the examiner refers to cytokines in general, not to a process involving a plurality of cytokines.

Claims 2, 4 and 50-53 continue to be rejected as obvious over Tamarkin et al. and Barrera et al. in view of van Emon et al. The latter reference is cited for its disclosure of affinity chromatography to remove targets. However, as above, neither Tamarkin et al. nor Barrera et al. disclose working with multiple target analytes, and van Emon et al. do not make up for this deficiency.

Claims 10, 18 and 19 are rejected as obvious over Tamarkin et al. and Barrera et al. in view of Posner et al. The latter reference is cited for teaching mixing of two or more different target analytes to prepare controls or calibrants. However, Posner et al. do not use materials where target analytes have been removed or are initially substantially not present. Relevance of Posner et al. is not seen to kits and the like such as those claimed. Additionally, Posner et al. are directed to controls, not to standard diluents.

Claims 9, 13, 14, 20-23, 25-28, 30, 31 and 55 are rejected over Tamarkin et al. and Barrera et al. in combination with Oliver et al. Oliver et al. is directed to a series of differentiable beads. However, since Tamarkin et al. and Barrera et al. only disclose working with a single analyte, there would be no need for the use of differentiable beads in their processes.

Claims 20-23, 37-31, and 55-57 stand rejected over Oliver et al. in view of Boguslaski et al. Oliver et al. is a brief disclosure of the use of the Luminex® bead system of the previously cited Chandler et al. patent, but does not specifically disclose the use of a single standard diluent that is lacking two or more target analytes. Boguslaski et al. do not make up for that.

Claims 24 is rejected over the combination of Tamarkin et al. and Barrera et al. with Oliver et al. and van Emon et al. However, for reasons mentioned above, this combination does not render claim 24 obvious.

Claim 54 is rejected as obvious over the combination of Tamarkin et al. and Barrera et al. in view of van Emon et al. and further in view of Vignali et al. Claims 58-60 are rejected over a combination of Oliver et al. and Boguslaski et al. in view of Vignali et al.

However, as with the previously discussed references, Vignali et al. do not disclose the use of a standard diluent as claimed herein.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Joel G. Ackerman
Reg. No. 24,307

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
JA:ja
60596265 v1